Quick guide

# Cannabinoid receptors

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***What are they?*** Cannabinoid receptors are G protein-coupled receptors with 7 transmembrane domains. They are expressed on the cell surface with their binding domain exposed to the extracellular space. To date, two cannabinoid receptors have been cloned, CB1 and CB2. Recent evidence suggests that a third 'CB3' receptor is out there, waiting to be cloned.

***Where are they?*** CB1 receptors are found in many brain regions including cortex, hippocampus, nucleus accumbens, basal ganglia, hypothalamus, amygdala, cerebellum and retina. CB2 is localized to immune system cells. Experiments in the hippocampus suggest that 'CB3' is there, but the presence or absence of 'CB3' in other brain regions remains to be determined.

***What turns them on?*** Δ9-tetrahydrocannabinol (THC), one of the psychoactive ingredients in marijuana, does a pretty good job, but more potent agonists such as the synthetic compound WIN55,212-2 (WIN), are available. Endocannabinoids also bind and activate cannabinoid receptors.

***What are endocannabinoids?*** THC and WIN are examples of *exogenous* cannabinoid receptor ligands, but the body makes its own ligands, too, and these are referred to as endocannabinoids. Two of the best-characterized endocannabinoids are anandamide and 2-arachidonylglycerol (2-AG). Other candidate endocannabinoids have been identified but which, if any, of these compounds are physiologically relevant cannabinoid receptor ligands is still an open question.

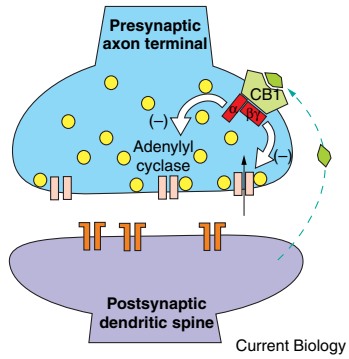


Figure 1. Depolarization of a postsynaptic neuron releases endocannabinoids. Binding of ligand to the CB1 receptor causes dissociation of the α and βγ subunits (red) of the G protein that is coupled to the receptor. The α subunit inhibits adenylate cyclase while the βγ subunits inhibit voltage-dependent calcium channels (pink) that control release of neurotransmitter-filled vesicles (yellow).

***Events downstream of cannabinoid receptors...*** Like other G protein-coupled receptors, binding of ligand to cannabinoid receptors causes dissociation of the α and βγ G protein subunits from the cannabinoid receptor and from each other. Release of the α subunit leads to inhibition of adenylyl cyclase, reducing cAMP levels in the cell. In neurons dissociated βγ subunits directly inhibit calcium channels that control neurotransmitter release. Effects on other ion channels have also been reported. In addition, there is evidence of a direct inhibitory effect on the transmitter release machinery.

***When do they get activated?*** Endocannabinoids are released in a calcium-dependent manner from dendrites, and maybe other parts of the cell, when neurons are activated. Endocannabinoids then travel backwards across the synaptic cleft, acting as retrograde messengers at cannabinoid receptors that are present on nearby presynaptic axon terminals.

***What effect does this have?*** Action potential-evoked neurotransmitter release is suppressed when cannabinoid receptors are activated. In the hippocampus, axon terminals that release inhibitory neurotransmitter are much more sensitive to endocannabinoids than terminals that release excitatory neurotransmitter, so moderate neuronal activity may preferentially reduce inhibitory input, while stronger activity could suppress both excitatory and inhibitory inputs. In the cerebellum, excitatory and inhibitory inputs seem to have about the same sensitivity to endocannabinoids.

***What happens if we don't have them?*** We don't know what happens in humans, but mice that have no CB1 receptors have improved memory, decreased appetite, a decreased tendency to become addicted to opiates, an increased sensitivity to pain, reduced locomotor activity, and shorter life spans than normal mice, suggesting a role for endocannabinoids in each of these systems.

***Where can I find out more?***

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